IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	TALWAR *et al.*	Atty. Docket No.:	RLL-1.1US
Application No.:	09/347,315	Examiner:	SPEAR, James M.
Filing Date:	July 2, 1999	Group Art Unit:	1615

For: ORALLY ADMINISTERED DRUG DELIVERY SYSTEM PROVIDING TEMPORAL AND SPATIAL CONTROL

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Commissioner for Patents
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Response to Office Action Mailed August 28, 2003

As of the date of this submission, claims 1-12 and 14-46 are pending. Of these, claims 33-46 are allowed, claims 3, 12, 17 and 19-31 are objected to, and claims 1, 2, 4-11, 14-16, 18 and 22 are rejected.

Rejection under 35 U.S.C. § 102(b) over Chavkin (United States Patent No. 4,613,497)

Claims 1, 2, 4-11, 14-16, 18 and 22 have been rejected as anticipated by Chavkin. This is a new rejection in the record of this application. Applicants respectfully traverse the rejection for the following reasons.

The Examiner is of the opinion that Chavkin discloses tablet compositions comprising a drug and means to provide sustained release of that drug. The Examiner further argues that particular polysaccharide gums disclosed in Chavkin (col 1, lines 43-48) are equivalent to applicant's viscosity enhancing agents. (Office Action, page 2).

The polysaccharide gums disclosed in Chavkin form complexes in combination with metal salts to form gels. The particular complexes formed in Chavkin compositions are made from a water soluble polysaccharide gum (sodium or potassium alginate, and kappa or iota carrageenan) and a gelling salt (the water soluble biocompatible calcium or postassium salts gluconate, lactate, chloride, or less soluble salts, carbonate or phosphate, if slower gelling is desired).

Examples I, II and VIII of Chavkin employ sodium alginate in combination with calcium gluconate. Example V of Chavkin employs sodium alginate in combination with dicalcium phosphate dehydrate.

The properties of these gelled complexes are well known. For example, the stabilities and swelling capacities of these gels are pH dependent. The publication Yotsuyanagi et al., "Calcium-induced Gelation of Alginic Acid and pH-sensitive Reswelling of Dried Gels," *Chem. Pharm. Bull.*, 35(4) (1987) 1555-63 (provided herewith as indicative of the information available to one of ordinary skill in the art), shows that "no swelling was observed in distilled water and in pH 1.6 KCl-HCl buffer, while in pH 7.0 phosphate buffer, the dried particle swelled to its original size in about 1 hour, followed by further swelling beyond its original size, and then it gradually disintegrated and dispersed over several hours. The results suggest that the dried gel particles keep their intact form in the stomach and when subsequently transferred to the intestine, the particles are likely to swell and function as matrices for controlled release of incorporated drugs." (Yotsuyanagi et al., page 1561, bottom to first line, page 1562).

Example III of Chavkin employs iota carrageenan in combination with calcium carbonate. Examples IV, VI and VII of Chavkin employ kappa carrageenan in combination with potassium gluconate.

The properties of these gelled complexes are also well known. For example, the stabilities of these gels are pH dependent. A printout from the website http://www.pformulate.com/carageenan.htm (provided herewith as indicative of the information available to one of ordinary skill in the art), shows that iota and kappa

carrageenans can form gels with calcium and potassium ions, respectively, but that "[n]one of the carrageenan types are stable in acid."

Thus, the complexes disclosed in Chavkin can only swell at relatively high pH, as compared to that found in the gastric environment. The compositions of Chavkin, being dependent on the formation of the complexes described above, cannot adequately swell in the stomach to be retained and provide the spatial control which is an aspect of applicants' claimed invention.

Thus, the applicants' claimed invention is not anticipated by the disclosure of Chavkin, and reconsideration and withdrawal of the anticipation rejection based on this reference is respectfully requested.

Respectfully submitted,

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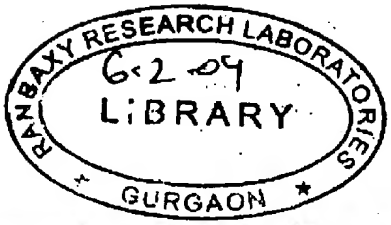

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Calcium-Induced Gelation of Alginic Acid and pH-Sensitive Reswelling of Dried Gels

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Calcium-induced alginate gelation was examined in terms of water content changes. The gelation was accompanied with considerable water loss, which reached about 50—60% (w/w) reduction in the fully-cured state. The calcium association with the polymer was strong enough to maintain the shape of fully-cured beads in distilled water and the amount of the ions associated with the alginate used in the present study was 1.6×10^{-3} mol/g of polymer. The diffusion coefficients of several model compounds having molecular weights ranging from 122 to 1050 were estimated as a function of the polymer concentration in the fully-cured beads.

The swelling property of dried gel particles prepared from fully-cured hydrogels was of interest: the particles remained unchanged in distilled water or acidic medium (pH 1.5 KCl–HCl), but swelled rather rapidly in pH 7.0 phosphate buffer to a size greater than their original size before being dried. Such a pH-sensitive swelling property could be advantageous for orally-administered drug vehicles, especially when an acid-sensitive drug is incorporated in the gel.

Keywords—alginic acid; calcium-induced alginate gel; dry gel swelling; pH-sensitive swelling; gel matrix; gel water content; controlled delivery

Although the definition of "gel" is controversial,[1] from a pharmaceutical point of view, gels can be regarded as semi-solid systems consisting of a lyophilic gel component which forms a three-dimensional network structure in which a liquid phase is constrained. Gel components used to prepare pharmaceutical vehicles include such synthetic and semi-synthetic polymers as carboxy vinyl polymer, hydroxyethylcellulose and hydroxypropylcellulose, in addition to the natural substances, pectin, tragacanth and alginic acid. These materials have generally been used as lyogels for topical application.

Alginic acid/Na-alginate, which is a polysaccharide found in brown algae, has a broad range of applications ranging from pharmaceutical and food adjuvant to an immobilization matrix for cells and enzymes due to its cation-induced gelation.[2-5] The polysaccharide can spontaneously form a translucent gel in association with calcium ions, and the mechanism of gelation, for which guluronic acid blocks are mainly responsible, has been intensively investigated by circular dichroism (CD) and nuclear magnetic resonance (NMR) studies.[6-10]

The purpose of this paper is to explore the possible applicability of alginate gel beads as orally-administered drug delivery vehicles. Because of the reswelling properties of alginate xerogels which are susceptible to surrounding pH, the following advantages may be envisaged: (1) acid-sensitive drugs are protected from gastric juice, (2) the reswelling process of xerogels in the intestine offers controlled-release drug delivery, (3) appropriately-sized particles of xerogels avoid local build-up of released drugs, (4) alginate is known to be nontoxic when taken orally.

several substances and reswelling behavior of dried gel particles.

Experimental

Materials——Na-alginate (lot no. AR01, Tokyo Kasei Kogyo, Tokyo) was used after dialysis against distilled water using Visking cellulose tubing (36/32) for 2 d (4 water replacements/d) followed by lyophilization. Calcium chloride dihydrate (special grade, Wako Chemicals, Osaka) was used. Benzoic acid and indigo carmine were purchased from Wako Chemicals. Bromocresol green was from Katayama Chemicals, Osaka, and rose bengal from Yoneyama Pharmaceuticals, Osaka. All other chemicals were of reagent grade.

Determination of Uronic Acid Residues——The following methods were used. (1) The Haug and Larsen method.[11] Briefly, alginate (50 mg) was mixed with 0.5 ml of 80% sulfuric acid and completely hydrolyzed for 18 h at 20 °C. After being neutralized by adding a slight excess of calcium carbonate, the hydrolysate was applied to an anion exchange column (Amberlite CG-400 Type 2, 20 cm × 2 cm i.d., Tokyo Yukikagaku Kogyo, Tokyo) to separate guluronic acid (G) and mannuronic acid (M). The fractions of each acid group were combined and the amount of each acid was determined by the orcinol method.[12] (2) The proportion of the homopolymeric fraction (GG plus MM) to the alternating (MG) fraction of alginate was determined by the phenol–sulfuric acid reaction method after partial acid hydrolysis with diluted hydrochloric acid.[13] (3) The proportions of GG and MM blocks were determined by NMR after partial hydrolysis.[14] (4) CD spectra of alginate were analyzed to assess the uronic acid composition (G to M) according to the peak/trough ratio method of Morris *et al.*[15] CD spectra of alginate dissolved in distilled water (0.8 mg/ml) were recorded on a CD spectropolarimeter (J-40A, JASCO, Tokyo) using a time constant of 4 s and a 10 mm pathlength. The proportions of GG, MM and MG blocks in Na-alginate used are shown in Table I.

Preparation of Alginate Gel Beads——Gel beads were prepared by dropping Na-alginate solution (1, 2, 3 and 4% (w/v) in distilled water) into $CaCl_2$ solution (0.02—0.1 M), using a peristaltic pump (MP-3, Tokyo Rikakikai Co., Tokyo) with a polyethylene-tubing nozzle (0.85 mm i.d. and 1.67 mm o.d.). The pumping rate was 0.11 ml/min. The falling distance was 3.5 cm. The weights of one droplet of the various alginate solutions were almost equal to each other, being 35.2±0.2 (S.D.) mg. The gel beads which were allowed to stand in the $CaCl_2$ solution for more than 300 h were assumed to be fully cured.

Weight Changes of Curing Gel Beads——Curing beads (10 beads) were taken out from the salt solution at appropriate intervals and weighted after the removal of surface moisture on filter paper. The weight of 10 droplets was assumed to be the initial weight at $t=0$. Instant curing at the immediate surface of the droplets made it possible to form almost spherical beads.

Determination of Calcium Contents in Fully-Cured Beads——Fully-cured gel beads formed in 0.1 M $CaCl_2$ were repeatedly washed for 24 h with fresh distilled water to remove excess calcium which was not associated with the gelation of alginate. A sample of gel beads was ashed after disintegration with ammonia water (0.001 M) as follows: the solution (0.5 ml) was placed in a 15 × 100 mm glass test tube to which 1 ml of sulfuric acid (6 N) was added, and heated on a heating block at 180 °C for 2 h. After cooling, 4—5 drops of hydrogen peroxide (30%) were added and the mixture was heated again at 180 °C for 1 h for final ashing. After cooling, the volume was appropriately adjusted by adding distilled water. The amount of calcium was then measured by using an atomic absorption analyzer (AA-630-12, Shimadzu, Kyoto) with reference to a calibration curve constructed with known amounts of $CaCl_2$.

Determination of Water Content in Fully-Cured Beads——Fully-cured beads were dried by various methods, heating in an oven at 110 °C overnight, drying in a silica gel desiccator for a week and natural drying at room temperature (R.H. 65%) for a week. The weight difference before and after drying was assumed to be the water content.

Determination of Diffusion Coefficients——The diffusion coefficients of benzoic acid (mol wt. 122.1), indigo carmine (466.4), bromocresol green (698.1) and rose bengal (1049.8) in various fully-cured beads formed in 0.1 M

Table I. The Composition of Alginate Used

Method[a]	Proportion (%)				
	M	G	MM	GG	MG
1	56.3	43.7			
2				50.2	49.8
3			72.5	27.5	
4	56.7	43.3			
Calc.[b]			36.3	13.9	49.8

a) See Experimental. b) Proportions calculated from the values obtained above.

$CaCl_2$ were estimated from the penetration rate of the substances into the beads, which were suspended in a well-stirred solution, based on the mathematical treatments of Crank applicable to diffusion in a sphere (see Appendix).[10] One hundred beads were introduced into a solution of each substance (1×10^{-4}—10^{-3} M, 10 ml of distilled water), and the concentration changes were followed with a perfusion cell system connected to a spectrophotometer (Hitachi 124, Tokyo). The temperature was 25 °C.

Swelling Rate of Dried Gel Particles——Fully-cured beads prepared with initial alginate concentrations of 2, 3 and 4% were dried at 110 °C overnight. The resulting dried particles were gently incubated in distilled water, pH 1.6 (KCl–HCl (0.2 M)) and pH 7.0 phosphate buffer (0.067 M) at 25 °C, and the diameter of each swelling particle, taken out of the solution, was measured with a micrometer. Because the shape of a swelling particle was not always perfectly spherical, the diameter was measured at three different positions of each particle and the average of five particles was calculated. The magnitude of swelling was represented by the ratio of the diameter of a swelling particle to the corresponding diameter of the fully-cured bead before drying.

Results and Discussion

Gelation Rate of Beads Measured in Terms of Weight Changes

When a droplet of the alginate solution contacted the $CaCl_2$ solution, gelation seemed to occur instantly on the surface of the droplet, which formed an almost spherical bead without splashing on contact. Soon the process could be visually detected as the appearance of a translucent spherical figure, followed by contraction of the figure. Although the intrinsic rate of curing is likely to be extremely fast, the apparent rate of spherical gel formation is primarily controlled by the penetration of calcium ions into the interior of droplets and therefore is dependent on the droplet size of alginate solution. Also water has to be squeezed out of the interior, traversing the already cured outer part to the bulk solution. It is therefore reasonable to consider that the overall rate of bead formation can be represented by the weight changes of the beads with time.

Figure 1 shows the weight changes of beads formed with various initial alginate concentrations in 0.1 M $CaCl_2$. The results indicate a rapid initial decrease and a subsequent slow stage: 60—70% weight loss out of the final weight loss occurred in the first several hours and it took about 70 h to reach constant weight. According to the CD study reported by Thom *et al.*,[6] spectral changes of alginate gelation by metal ions continued for 15—20 d. It seems that the apparent gelation is finished rather quickly on the basis of gel weight but fine rearrangement of the gel structure continues for a long time.

The weight of curing beads should be the sum of the weights of the calcium-associated polymer and water, but the contribution of the metal ions was negligible even for fully-cured beads, as described later. The total weight loss is assumed to be solely due to the amount of

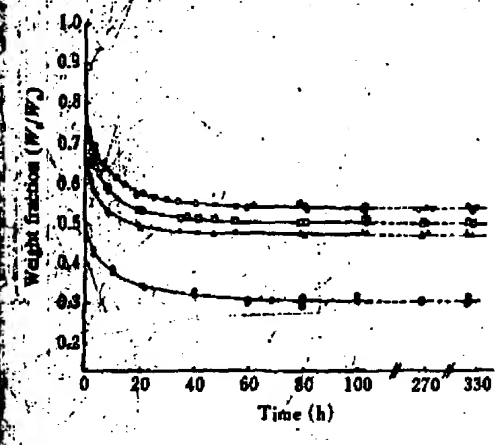


Fig. 1. Weight Fraction Changes of Curing Beads in 0.1 M $CaCl_2$

W_0, weight of 10 droplets of alginate solution ($t=0$); W_t, weight of 10 beads at time t. Initial alginate concentrations: ○, 4% (w/v); □, 3; △, 2; ○, 1. Temp., 25 °C.

water squeezed out of the beads. If the process of curing proceeds concentrically from the surface of a droplet to the center, squeezing out interior water, the amount of water leached out would be related to the third power of the radius as the contraction proceeds, *i.e.* the further out a hypothetical concentric segment in the sphere, the greater the volume of water squeezed out, resulting in a more rapid weight loss in the early stages. It was furthermore noted that the rate of the subsequent slow stages was similar irrespective of the initial alginate concentration. This result indicates that the cured structures of the hydrogels are loose enough for water to traverse to the outside bulk solution. As the consequence of water loss, the initial alginate concentration should be increased in the beads. Accordingly, the alginate concentration in the fully-cured beads may have to be corrected.

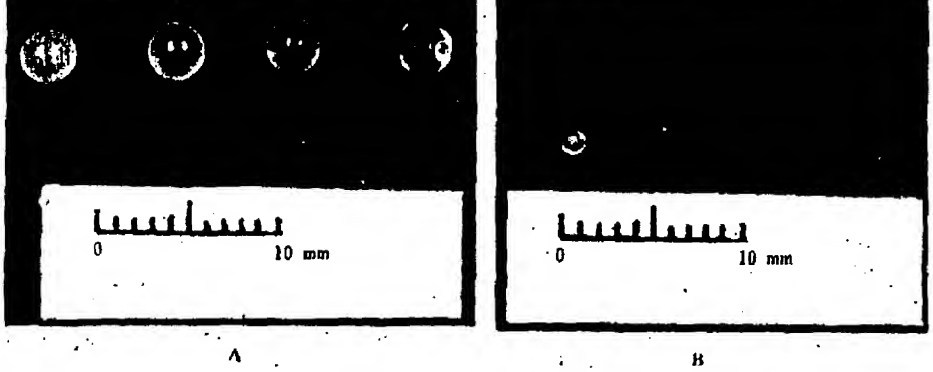
The Magnitude of Contraction to Form Fully-Cured Gel Beads

Table II summarizes the effect of $CaCl_2$ concentration on the weight fraction of fully-cured gel beads formed with various initial alginate concentrations. The amount of water squeezed out reached about 50%. The weight of beads decreased with increasing $CaCl_2$ concentration and appeared to become constant at salt concentrations above 0.08 M, suggesting that the fully-cured state depends on the bulk $CaCl_2$ concentration and a threshold bulk $CaCl_2$ concentration is required for the ultimately-cured condition, *i.e.* in this case

Table II. Weight Fractions of Fully-Cured Gel Beads Formed with Various Combinations of Initial Alginate Concentration and $CaCl_2$ Concentration

Initial alginate concn. (%, w/v)	Weight fraction (W_e/W_0)			
$CaCl_2$ concn. (M)	0.02	0.05	0.08	0.1
1	...[a]	—[a]	[a]	0.306[b]
2	0.545	0.501	0.467	0.472
3	0.590	0.571	0.502	0.493
4	0.712	0.633	0.539	0.536

W_0, weight of droplets (assumed at $t = 0$); W_e, weight of fully-cured beads ($t = 270$–330 h).
[a] Incomplete gelation. [b] Incomplete beads.



A B

Fig. 2. Photographs of Fully-Cured Beads in 0.1 M $CaCl_2$ (A) and a Dried Gel Particle (110 °C) (B)

A, initial alginate concentrations from the left, 4% (w/v), 3, 2, and 1; B, 4% (w/v).

Table III. Physical Dimensions of Fully-Cured Gel Beads Formed in 0.1 M Calcium Chloride

Initial alginate concn. (%, w/v)	Radius[a] (mm)	Weight[a] (mg/bead)	Volume (mm^3/bead)	Density
1	—	15.6	—	—
2	1.55	16.7	15.6	1.07
3	1.59	17.7	16.8	1.05
4	1.60	18.7	17.2	1.09

a) Average of 10 beads.

0.08 M. If the amount of $CaCl_2$ were in excess of the amount of alginate, as was the case in this study even for 0.02 M $CaCl_2$, the weight changes should converge to the values of 0.1 M $CaCl_2$ provided that the initial alginate concentration was kept constant. It was assumed that the greater contraction of the beads with increasing $CaCl_2$ concentration is mainly due to the increase of dehydration from alginate molecules.

As the initial alginate concentration was increased, a weight increase was generally observed, probably due to increasing density of the beads. Figure 2 shows typical fully-cured beads (in 0.1 M $CaCl_2$) with almost completely spherical shape, from which the physical dimensions were obtained as shown in Table III. The radius of the beads, and hence the volume, was little affected by the initial alginate concentration, but a higher initial concentration resulted in more translucent beads. This means that the greater the initial concentration, the denser the fully-cured state of the gel structure.

As shown in Table II, a considerable amount of water was squeezed out during the curing process. Thus, the final alginate concentration in fully-cured beads should be much higher than the initial polymer concentration. The final concentration was calculated from the weight fraction changes of fully-cured beads: 2% initial concentration increased to 4.2% (w/w), 3% to 6.1% and 4% to 7.5%. Alternatively, the w/v expression calculated from the final volume and the density gave 4.5% (w/v), 6.4% and 8.2%, respectively.

Calcium Content in Fully-Cured Beads

Before assaying Ca^{2+} involved in the gelation, the beads were subjected to repeated washing with distilled water to remove unassociated Ca^{2+}, during which their physical appearance remained unchanged. This indicates that the association of Ca^{2+} with the polymer is strong, being barely affected in distilled water but completely destroyed by ethylenediaminetetraacetic acid (EDTA).

Figure 3 shows a plot of the Ca^{2+} content in fully-cured beads (in 0.1 M $CaCl_2$), *i.e.* ultimately-cured beads, against the final alginate concentration (w/w). The amount of Ca^{2+} involved in the gelation was proportional to the alginate concentration and there was no interference by coexisting sodium ions, indicating that Ca^{2+} is quantitatively and specifically associated with the polymer molecules. From the slope of the linear plot, the amount of Ca^{2+} associated with the polymer molecules was found to be 1.6×10^{-3} mol/g of polymer. As mentioned earlier, the contribution of the calcium association to the weight changes in the curing process of beads was negligible.

Water Content in Fully-Cured Beads

The water content held in fully-cured beads was estimated from the weight difference between hydrogel and xerogel dried under various conditions. Figure 4 shows the relation between the water content and the calculated polymer concentration (w/v). The water content was inversely proportional to the polymer concentration but was dependent on the drying

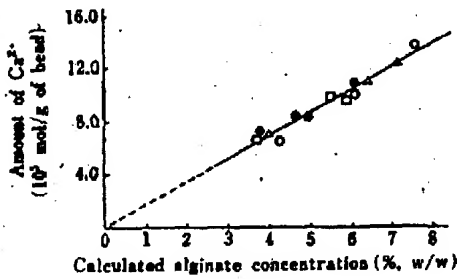


Fig. 3. The Amount of Ca^{2+} Associated with Fully-Cured Beads

○, formed in 0.1 M $CaCl_2$; △, 0.1 M $CaCl_2$ and 0.1 M NaCl; □, 0.1 M $CaCl_2$ and 0.15 M NaCl; ●, 0.1 M $CaCl_2$ and 0.2 M NaCl. The abscissa indicates the alginate concentration (w/w) calculated from the data of Fig. 1.

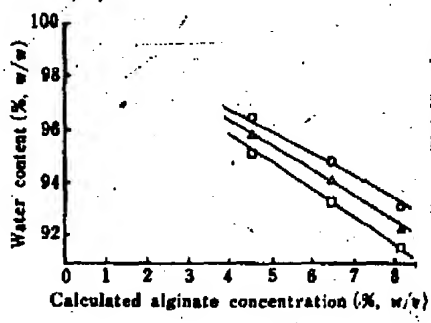


Fig. 4. Water Contents in Fully-Cured Beads in 0.1 M $CaCl_2$

Drying methods: ○, dried at 110 °C; △, silica gel in a desiccator; □, natural drying. The abscissa indicates the alginate concentration (w/v) calculated from the data of Fig. 1 and Table III.

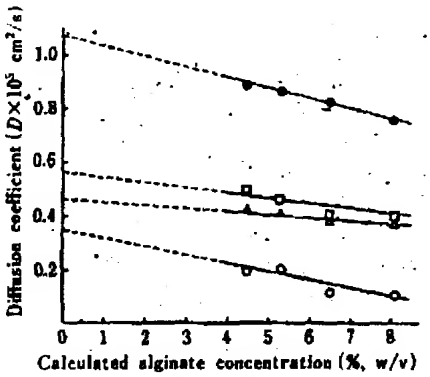


Fig. 5. Diffusion Coefficients of Various Substances in Fully-Cured Beads

●, benzoic acid; □, indigo carmine; △, bromocresol green; ○, rose bengal. Temp., 25 °C. The abscissa indicates the alginate concentration (w/v) calculated from the data of Fig. 1 and Table III.

method. Drying at 110 °C seemed to remove all of the water entrapped in the hydrogels because the weight of dried gel corresponded to the amount of polymer in the initial droplet. Drying over silica gel in a desiccator gave slightly lower values, *i.e.*, it was less effective. The resulting gel particles had a relatively round shape with a smooth surface (Fig. 2), and were extremely hard; it was difficult to crush them in an agate mortar.

Diffusion Characteristics of Substances in Fully-Cured Beads

The diffusion behavior of substances in gels is one of the important aspects to be considered when the gel beads are to be used as a drug delivery system. Several substances of various molecular weights such as benzoic acid (mol wt. 122), indigo carmine (466), bromocresol green (698) and rose bengal (1050) were selected as model compounds. Based on the mathematical treatment for diffusion in a sphere,[16] the diffusion coefficient was calculated from the penetration rate into the beads in well-stirred solution.

Figure 5 shows a plot of the diffusion coefficient obtained against the alginate concentration (w/v) calculated in the fully-cured beads (in 0.1 M $CaCl_2$). The diffusion coefficient became smaller as the polymer concentration increased, though the dependency on the polymer concentration was apparently similar irrespective of the molecular weights of

TABLE IV. Estimated Diffusion Coefficient in Water and the Concentration Ratio between Bulk Solution and Gel Beads (25 C)

Drug	D_w (10^5 cm^2/s)	$R^{a)}$
Benzoic acid	1.07	1.02
Indigo carmine	0.555	1.03
Bromocresol green	0.448	1.03
Rose bengal	0.328	2.33

a) R = concentration in gel beads/concentration in bulk solution at equilibrium. The beads were prepared at an initial alginate concentration of 2% with 0.1 M $CaCl_2$.

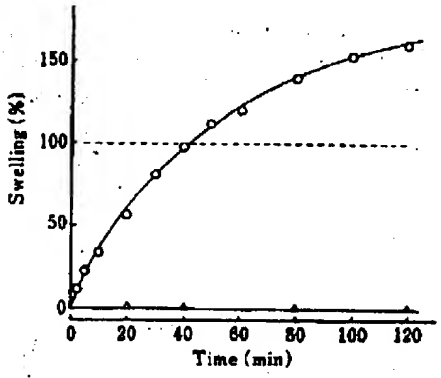


Fig. 6. The Swelling Rate of Dried Gel Particles in Aqueous Solutions

○, pH 7.0 phosphate buffer; △, pH 1.5 KCl–HCl buffer. Temp., 25 °C. The dotted line (100%) indicates the size of the original hydrated bead (diameter). The sample particles were prepared with an initial alginate concentration of 4% and 0.1 M $CaCl_2$, and were dried at 110 °C.

these substances. The diffusion coefficients in water were estimated by extrapolation to the ordinate (Table IV). The value of benzoic acid thus estimated agrees well with the literature value of 1.03×10^{-5} cm^2/s.[17]

In the beads prepared with the initial concentration of 4%, *i.e.* 8.2% in the fully-cured state, the diffusion coefficients of benzoic acid, indigo carmine and bromocresol green were reduced to about 70—80% of the respective aqueous diffusion coefficients, while that of rose bengal was reduced to about 30%. As shown by the concentration ratio of the bulk aqueous phase and the gel beads determined at equilibrium (Table IV), these substances other than rose bengal were little associated with the polymer molecules. The interaction of rose bengal with the polymer molecules would have apparently given a higher value of D_w than the actual value, since the calculation was made under the assumption that no interaction occurs.

Swelling of Dried Gel Particles

The swelling behavior of dried gel particles in aqueous solution was followed by measuring the diameter of the swelling particles with time. Figure 6 shows the magnitude of swelling in various aqueous environments where the magnitude is represented by the ratio of the diameter of swelling particles to that of the fully-cured hydrated beads. The value of 100% indicates that a swelling particle reached the original size of the hydrated bead before being dried. It should be noted here that no swelling was observed in distilled water and in pH 1.6 KCl–HCl buffer, while in pH 7.0 phosphate buffer the dried particle swelled to its original size in about 1 h, followed by further swelling beyond its original size, and then it gradually disintegrated and dispersed over several hours. These results suggest that the dried gel particles keep their intact form in the stomach and when subsequently transferred to the intestine, the particles are likely to swell and function as matrices for controlled-release of

incorporated drugs.

There was little difference in the rate of swelling among the gel particles prepared at various initial alginate concentrations, 2—4%. This result, however, may be confined to the size range of dried particle examined in the present study. Because the swelling rate should be related to the penetration rate of water into the porous gel structure, particles much smaller in size would swell at faster rates.

Such a pH-sensitive swelling property of the alginate gel particles means that an acid-sensitive drug incorporated may be effectively shielded from the attack of gastric juice and be released at desirable rates from the particles in the intestine. However, further studies are needed for the rational design of controlled-release alginate matrices.

Appendix

When a spherical bead having a diameter a, which is free from solute, is suspended in a well-stirred solution with an initial solute concentration of C_0 and a volume V, the amount of solute, M_t, in the sphere after time t can be represented as a fraction of the corresponding quantity after infinite time, M_∞, by the following equation[10]:

$$\frac{M_t}{M_\infty}=1-\sum_{n=1}^{\infty}\frac{6\alpha(1+\alpha)\exp(-Dq_n^2t/a^2)}{9+9\alpha+q_n^2\alpha^2} \tag{1}$$

where the q_n's are the non-zero roots of

$$\tan q_n=\frac{3q_n}{3+\alpha q_n^2} \tag{2}$$

α is the ratio of the volumes of solution and bead, $3V/4\pi a^3$, and D is the diffusion coefficient. The parameter α can be expressed in terms of the final fractional uptake of solute by the bead, as follows:

$$\frac{M_\infty}{VC_0}=\frac{1}{1+\alpha} \tag{3}$$

The solute concentration in the bulk solution may be expressed as follows:

$$C_b=\frac{\alpha C_0}{1+\alpha}\left[1+\sum_{n=1}^{\infty}\frac{6(1+\alpha)\exp(-Dq_n^2t/a^2)}{9+9\alpha+q_n^2\alpha^2}\right] \tag{4}$$

where C_b is the solute concentration in the bulk phase.

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EXCIPIENTS

Carrageenan

*1] **Description:*** Naturally occurring family of polysaccharides derived from red sea weed. Three basic types are available: Kappa, iota and lambda which differ in the number and location of sulfate ester substitution. These are available in a variety of grades that provide a wide range of rheology properties for gelling and viscosifying preparations.

None of the carrageenan types are stable in acid. Hydrolysis in low pH systems is accelerated by heat. In the gel state, kappa and iota carrageenans are stable above a pH of 3.8.

*2] **Properties:***

IOTA Carrageenans	*Viscosity*	*Gel Type*	*Solubility*	*Reactivity*
Gelcarin® GP-379NF	High Thixotropic	Elastic Medium strength Forms strongest gel with calcium ions	hot water soluble Sodium salt soluble in cold water. Calcium salt cold water swellable to form a thixotropic dispersion.	Polyol and protein reactive
SeaSpen® PF	Medium Thixotropic	Elastic Weak strength Forms strongest gel with calcium ions	cold water soluble, delayed gel formation	

KAPPA Carrageenans	Viscosity	Gel Type	Solubility	*Reactivity*
Gelcarin® GP-812NF	Low	Brittle Strong strength Forms strongest gel with potassium ions	Hot water soluble Sodium salt soluble in cold water. Potassium, calcium and ammonium salt cold water swellable.	
			Hot water	

Gelcarin® GP-911NF	Low	Brittle Firm strength Forms strongest gel with potassium ions	soluble Partially soluble in cold water Sodium salt soluble in cold water. Potassium, calcium and ammonium salt cold water swellable.	Polyol and protein reactive

LAMBDA Carrageenans	Viscosity	Gel Type	Solubility	*Reactivity*
Viscarin® GP-109NF	Medium	Non-gelling	Hot water soluble Partially soluble in cold water	Polyol and protein reactive
Viscarin® GP-209NF	High	Non-gelling	Hot water soluble Partially soluble in cold water	Polyol and protein reactive

Kappa/Lambda carrageenans mix	*Viscosity*	*Gel Type*	*Solubility*
Viscarin® GP-328NF	Medium-high	weak	Hot water soluble

3] Applications:

Gelling agent	Kappa and iota types set up gel structures that are thermally reversible. Kappa creates a stiff, strong gel, useful in applications that require shape retention such as otic, vaginal, suppository, and controlled release dosage forms. Iota gels are flexible, elastic gels which when broken will reheal into a gel structure, useful in film formation or spreading applications Genugel and Genuvisco are used for softgellingin capsules
	Gelcarin® GP-379NF for suspensions at levels of 0.3 - 1.0%. SeaSpen® PF is useful for suspensions and

Suspensions	reconstitutable suspensions at levels of 0.5 - 1.0%. Delayed gelling properties enable ingredient distribution in the system before a gel structure is established. After set up of the gel a stable suspension of drug is obtained.
Viscosifying agent	Lambda carrageenans such *Viscarin® GP-109NF and Viscarin® GP-209NF* are good viscosifying agents *at levels of 0.1 - 1%*. Viscosity can be controlled by the use of metal ions.
Topical gels, creams and lotions	All carrageenans have excellent water binding capabilities which are useful in topical dosage forms. They are non-sticky, and provide pleasant skin feel. Gelcarin® GP-379NF for creams at *levels of 0.3 - 1.0%.* Gelcarin® GP-812NF for gels at levels of 0.3 - 1.0%. Viscarin® GP-109NF and *Viscarin® GP-209NF* for creams and lotions at levels of 0.1 - 1%. *Viscarin® GP-328NF for creams and lotions at levels of 0.7 - 1.2%. Excellent for maintaining emulsions.* *SeaSpen® PF for lotions and creams at levels of 0.5 - 1.0%.*

4] Suppliers:

CPKelco	Genugel Genuvisco
FMC	Gelcarin®, NF
	Viscarin®, *NF*
	SeaSpen®, PF

Need a supplier? Submit in Requests!!!

5] References:

Gelcarin® and Viscarin® Carrageenan, NF, Technical Bulletin online at www.avicel.com

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